

**TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES
ADVISORY COMMITTEE MEETING**

February 12 and 13, 2004

Silver Spring, MD

Issue Summary, Topic #4.A.a.

**Current Safeguards for Blood Products:
Approach to products containing or exposed to bovine materials**

Subtopics:

- 1. Current FDA Regulatory Approach to Blood Products Containing or Exposed to Bovine Materials**
- 2. Approach of the European Agency for the Evaluation of Medicinal Products (EMA) to Blood Products Potentially Exposed to TSE agents**

1. Current FDA Regulatory Approach to Blood Products Containing or Exposed to Bovine Materials

Background

Blood products may contain or have been exposed to bovine materials during manufacturing. FDA has requested, in a series of letters since 1992, that manufacturers source most bovine materials used in the manufacture of FDA-regulated products from non-BSE countries. Since BSE has spread beyond the U.K. and continental Europe, it has become increasingly difficult to ensure consistent sourcing of all bovine materials from BSE-free areas. Switching sources of manufacturing reagents to new countries, and potentially to new suppliers, requires time for arrangements to be made and to qualify new raw materials. Furthermore, as the number of countries with reported BSE increases, the supply of suitable bovine material available from BSE-free countries may become inadequate to support manufacturing needs.

Types of Bovine Materials Used in Blood Products and Blood Product Manufacturing

Many blood products are exposed to bovine material during manufacturing. These include topical hemostatic agents, plasma-derived coagulation products, recombinant coagulation products, and immune globulins. Licensed products that contain bovine components include Bovine Thrombin and Fibrin Sealant, which contain bovine serum proteins, and bovine aprotonin.

Examples of bovine materials used in manufacturing of blood products include:

Bovine Material	Use	Tissue Source
Fetal Bovine Serum	Tissue Culture	Serum
Albumin	Tissue Culture	Plasma
Insulin	Tissue Culture	Pancreas
Aprotonin	Tissue Culture	Lung
Tallow	Polysorbate 80 – viral inactivation	Fat

Clearance of TSE Agents During Manufacturing of Blood Products

Published studies have demonstrated that, under specific conditions, TSE agents may be partitioned or removed from blood products during certain manufacturing processes; the TSEAC most recently reviewed a summary of published and unpublished studies on February 20, 2003.¹ Different specific conditions of manufacturing, such as protein concentrations and matrices, pH, ionic strengths, and filter types (depth and membrane filtrations) may affect the degree of TSE agent removal in experimental studies. Most experimental studies have used TSE-agent-infected brain tissue as spiking agents, because infectivity in blood of experimental animals, when detected at all, is in very low concentration. TSE agent removal has been demonstrated with specific processes and in specific contexts, for example: ethanol precipitation, glycine precipitation, PEG precipitation, depth filtration, nanofiltration, and ion exchange chromatography (see appendix for publication list).

FDA Actions to Minimize the Risk of TSE Agents in Blood Products

FDA has articulated the following policies regarding blood products:

- ?? Recommended that blood and plasma programs defer donors for geographic risks of BSE exposure based on location and duration of the exposure, for history of transfusion in the U.K. since 1980, and for injection of bovine insulin sourced in the U.K. since 1980²
- ?? Recommended that blood components be retrieved and quarantined if a donor later develops CJD or vCJD. (Retrieval for plasma derivatives is recommended only in cases of vCJD in the donor.)
- ?? Requested manufacturers to source bovine materials from non-BSE countries and to seek alternatives to use of bovine materials
- ?? Encouraged studies of TSE agent clearance by manufacturers (At its February 2003 meeting, TSEAC endorsed FDA consideration of labeling claims for TSE agent clearance in plasma derivatives, based upon specific demonstration of TSE agent removal during manufacturing.¹)

¹ TSEAC February 20, 2003 transcripts and materials at

<http://www.fda.gov/ohrms/dockets/ac/cber03.html#TransmissibleSpongiform>

² Guidance to Industry “Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products” at <http://www.fda.gov/cber/gdlns/cjdvcjd.htm>

In addition to these measures, labeling of plasma derivatives provides risk communication. FDA has recommended that the warnings section of the package insert for blood components and blood products should read: “Because this product is made from human blood, it may carry a risk of transmitting infectious agents, e.g. viruses, and, theoretically, the Creutzfeldt-Jakob disease agent.”²

2. Approach of the European Agency for the Evaluation of Medicinal Products (EMA) to Blood Products Potentially Exposed to TSE agents

In February 2003, EMA published a position statement entitled “CPMP Position Statement on CJD and Plasma-Derived and Urine-Derived Medicinal Products.”³ This paper offered several recommendations:

- ?? Recommended deferral as donors of persons who had spent at least one year in the U.K. between 1980 and 1996,
- ?? Stated that it is “highly desirable for manufacturers to undertake product-specific investigational studies of key steps” [of a production process],
- ?? Recommended withdrawal of plasma derivatives if a donor to the plasma pool has subsequently developed vCJD,
- ?? Encouraged optimal use of plasma products,
- ?? Did not recommend donor deferrals for urine-derived medicinal products, based upon a lack of epidemiological or laboratory evidence suggesting that urine contains infectivity. (However the document noted that the issue of risk of urine-derived products was to be kept under review.)

In November 2003, the EMA published a discussion paper entitled “The Investigation of Manufacturing Processes for Plasma-derived Medicinal Products with Regard to vCJD Risk.”⁴ This document was intended to “provide a basis for development of a ‘points to consider’ document on how to investigate manufacturing processes with regard to vCJD risk.” The discussion paper proposed guidelines for TSE clearance studies, including the following:

- ?? Use of actual production material for experiments is recommended.
- ?? Scaled-down laboratory models are ordinarily appropriate.

³ CPMP position statement on CJD and plasma-derived and urine-derived medicinal products, at <http://www.emea.eu.int/index/indexh1.htm>, go to Guidance Documents, then TSE, then Guidance, and select CPMP Position Statement on Creutzfeldt-Jakob disease and Plasma-derived and Urine-derived Medicinal Products

⁴ <http://www.emea.eu.int/index/indexh1.htm>, go to Guidance Documents, then TSE, then Guidance, and select Discussion Paper on the Investigation of Manufacturing Processes for Plasma-Derived Medicinal Products with Regard to VCJD risk.

- ?? The spiked infectious material should not comprise more than 10% ?? of the final volume.
- ?? Studies should be conducted according to Good Laboratory Practices (GLP).
- ?? Partitioning of infectivity should be demonstrated.
- ?? Infectivity reduction factors < 1 log should be considered insufficient.
- ?? Combined-step studies should help to support a decision to accept the additivity of two or more steps having reduction factors of moderate magnitude.
- ?? Combined steps are helpful where some step might significantly alter the context or physical state of TSE-agent-containing material (e.g., after solvent-detergent treatment), possibly affecting removal by a subsequent step.
- ?? A rationale should be provided for selection of the spiking TSE agent strain; rodent models are generally acceptable.
- ?? While a microsomal fraction may be preferred, other membrane-bound spikes may also be used, with a caveat that the actual physical form of TSE agent infectivity in blood remains unknown. A rationale should be provided for the form of spiking agent selected.
- ?? Bioassays for infectivity are suggested to confirm clearance of TSE agent, but PrP^{Sc} assays may also be used to identify for further study those steps most likely to remove infectivity or as a surrogate assay for infectivity (when proven for the particular model used).
- ?? Studies should focus first on products manufactured by processes that appear to have the lowest overall capacity to remove TSE agents.
- ?? Due to a lack of studies specifically relevant to plasma processing equipment, the discussion paper does not offer specific recommendations on this topic.

Following the recent report of a presumptive transfusion-transmitted case of vCJD in the U.K., the EMEA convened a workshop to reevaluate the potential risk of human TSEs for blood products (January 28-29, 2004). Highlights of the workshop will be summarized when available.

Appendix

Experimental Studies of TSE Agent Clearance in Blood Product Manufacturing Processes

1. Brown, P et al, *Transfusion* 1998 38:810-6
2. Brown, P et al, *Transfusion* 1999 39: 1169-78
3. Lee, DC et al, *J. Virol. Meth.* 2000 84: 77-89
4. Foster, PR et al, *Transfusion Science* 2000 22:53-56
5. Foster, PR et al, *Vox Sanguinis* 2000 78:86-95
6. Lee, DC et al, *Transfusion* 2001 41: 449-55
7. Cai, K et al, *Biochem Biophys. Acta* 2002 1597: 28-35
8. Stenland, JS et al, *Transfusion* 2002 42:1497-1500
9. Vey, M et al, *Biologicals* 2002 30:187-96
10. Reichl, HE et al, *Vox Sanguinis* 2002 83:137-45
11. Trejo, SR et al, *Vox Sanguinis* 2003 84:176-87

12. Van Holten, RW et al, Vox Sanguinis 2003 85:20-24

Attachments

1. FDA Guidance: Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products, January 2002
2. EMEA/CPMP Discussion Paper on the Investigation of Manufacturing Processes for Plasma-Derived Medicinal Products with Regard to VCJD risk
3. EMEA/CPMP Position Statement on Creutzfeldt-Jakob disease and Plasma-derived and Urine-derived Medicinal Products